Effect of time to treatment and age on one year mortality in acute STEMI: difference between thrombolysis and primary percutaneous coronary intervention

Quelle place pour la thrombolyse dans les syndromes coronaires aigus avec sus-décalage du segment ST ?

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Summary

Context. — Although thrombolysis (THL) and primary percutaneous coronary intervention (PPCI) are two validated options in reperfusion algorithms for ST-elevation myocardial infarction (STEMI), recent papers seems to show that PPCI could be the best therapeutic option irrespective of the time to treatment (TT) and of the cardiovascular risk profile of the patient. The impact of TT and age on reperfusion strategies requires elucidation. The aim of this study was to analyze the effect of time to treatment and age on the 1-year mortality of patients presenting with STEMI, for each reperfusion strategy.

Materials and methods. — The study population consisted in 794 patients directly admitted to the cardiological intensive care unit for STEMI ≤ 12 hours. The relationship between TT and 1-year mortality was studied using logistic regression models. The models were implemented on the overall population and on 3 different age groups: [≤ 65 years]; [≥ 65 and < 75 years]; [≥ 75 years] for patients undergoing THL (n=299) and for patients undergoing PPCI (n = 495). There was no significant between-group difference in all-cause 1-year mortality for the patients [≤ 65 years] and those [≥ 65 and < 75 years]. In contrast, the 1-year mortality was significantly higher in the patients [≥ 75 years] undergoing THL (51.4 vs. 15.3%; p<0.001). The analysis of the curves of mortality suggests that 1-year mortality of patients with STEMI depend not only on reperfusion strategy but so on the time to treatment and on the age of the patients.
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Introduction

Various recommendations advise using primary percutaneous coronary intervention (PPCI) for all patients with ST-elevation myocardial infarction (STEMI) ≤12 hours when PPCI can be conducted within 90 minutes of the initial medical contact. In other cases, thrombolysis (THL), particularly pre-hospital THL, is to be preferred in the absence of contra-indication. In other respects, age is not clearly included in these algorithms proposed in these recommendations (1-3). Recently, a large-scale study including pre-hospital THL have demonstrated that PPCI may be superior to THL irrespective of the time of treatment (TT) and of the age of the patients (4) whereas another one showed that reperfusion algorithm could also depend on patient age, on the TT and on STEMI topography (5). Thus, the impact of time to treatment and age on reperfusion strategies requires elucidation. The aim of this study was to analyze the effect of time to treatment and age on 1-year mortality in patients presenting with STEMI, for each reperfusion strategy.

Materials and methods

Population

The data were derived from a single-center, prospective, exhaustive STEMI registry. In order to define the study population, 1648 admissions for STEMI ≤12 h between 1995 and 2005 were analyzed. All the patients included in the study had, on an ECG recording, in at least 2 contiguous leads, an ST-segment elevation ≥1 mm in the bipolar leads or ≥2 mm in the precordial leads. In order to prevent bias, patients transferred from other centers were excluded due to the very variable time intervals between THL administration and rescue PCI implementation (n = 508). Similarly, patients presenting with cardiogenic shock on admission were excluded since PPCI is known to be superior to THL (n = 37). Patients who did not undergo reperfusion therapy in the acute phase due to a non-contributive ECG or because they were considered too frail for that therapy were also excluded (n = 269). Forty patients were lost to follow-up (n = 40). In all, 794 patients were included in the analysis (figure 1). All the patients received aspirin, heparin and clopidogrel in the absence of any contra-indication. In the THL group, various thrombolytics were used: streptokinase, alteplase and tenecteplase. If THL efficacy was not patent at 90 min (persistent pain or non-resolution of ST-segment elevation), angiographic control was performed and rescue PCI implemented if the TIMI flow was < 3. In other cases, the patient underwent coronary angiography after a few days and was reperfused according to the ischemia test data. PPCI was considered as successful when a TIMI 3 flow grade and a less than 30 per cent residual stenosis was obtained. In these patients abciximab was used since 2000. Only the culprit artery was treated during the acute phase. The other arteries were treated secondarily by PCI or bypass as a function of the ischemia test results. TT was defined as the interval between symptom onset and thrombolytic administration for patients treated by THL and as the interval between symptom onset and balloon deployment for patients treated by PPCI. Left ventricular...
ejection fraction was determined either with echocardiography or with angiography.

**Statistical analysis**

THL and PPCI were compared using Student's t-test (or Wilcoxon's test, if necessary) and the chi² test (or Fisher's exact test if necessary). The analysis was conducted on the whole population, then on the 3 age groups: [< 65 years]; [≤ 65 and < 75 years]; [≥ 75 years]. Logistic regression models were used to evaluate the association between 1-year mortality and time to treatment. The analyses were stratified by reperfusion type: THL or PPCI. The analyses were conducted on the whole population and on the age subgroups. All the analyses were conducted using the SAS 8.1 software (Cary, NC).

**Results**

**Characteristics of the patients on admission and prognosis (table 1)**

Out of the 1648 cases of STEMI between 1995 and 2005, 794 cases were included in the analysis. Of those patients, 495 were treated by PPCI and 299 by THL. The baseline characteristics of the patients were similar except for the significantly higher age in the PPCI group. The subgroup analysis of the age groups did not show any significant difference. In the PPCI group, abciximab was used in 42% of cases. Final angiographic success was obtained in 92.5% of the cases. THL treatment was administered in pre-hospital setting in 6.6% of patients in this group. Rescue PCI was implemented in 22.4% of cases. Control coronary
Table 1  Patient characteristics and outcome by age group and reperfusion strategy

<table>
<thead>
<tr>
<th></th>
<th>overall (y)</th>
<th>&lt; 65 y</th>
<th>65-74 y</th>
<th>&gt; 75 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPCI N = 495</td>
<td>THL N = 299</td>
<td>PPCI n=241</td>
<td>THL n=181</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63.2 ± 13.7</td>
<td>60 ± 12.3*</td>
<td>51.2±7.7</td>
<td>52±7.9</td>
</tr>
<tr>
<td>Men (%)</td>
<td>78.2</td>
<td>83.3</td>
<td>90.4</td>
<td>92.3</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>57</td>
<td>58.5</td>
<td>73.4</td>
<td>69.6</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>40.8</td>
<td>33.8</td>
<td>33.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>61.6</td>
<td>57.5</td>
<td>70.5</td>
<td>63.5</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16.6</td>
<td>11.7</td>
<td>13.3</td>
<td>7.8</td>
</tr>
<tr>
<td>Previous infarction (%)</td>
<td>9.1</td>
<td>10.7</td>
<td>8.7</td>
<td>10.5</td>
</tr>
<tr>
<td>Prior CABG or PCI (%)</td>
<td>8.3</td>
<td>5.4</td>
<td>4.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Killip class on admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/2/3</td>
<td>81.3/14.2/4.5</td>
<td>84.2/14.4/1.3</td>
<td>89.6/7.9/2.1</td>
<td>87.3/11.6/0.5</td>
</tr>
<tr>
<td>Anterior infarction (%)</td>
<td>42</td>
<td>38.8</td>
<td>38.2</td>
<td>37.6</td>
</tr>
<tr>
<td>number of diseased vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/2/3</td>
<td>50.7/31.3/18</td>
<td>50.4/29.3/20.4</td>
<td>58.9/26.3/12.9</td>
<td>56.3/24.9/13.2</td>
</tr>
<tr>
<td>Gp 2b/3a inhibitors (%)</td>
<td>42</td>
<td>1</td>
<td>44.8</td>
<td>1.6**</td>
</tr>
<tr>
<td>Stenting (%)</td>
<td>58.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI success (%)</td>
<td>92.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rescue PCI (%)</td>
<td></td>
<td></td>
<td>22.4</td>
<td>25.9</td>
</tr>
<tr>
<td>LVEF at discharge (%)</td>
<td>46.3 ± 9.6</td>
<td>47.7±11.8</td>
<td>47.0±9.4</td>
<td>48.2±12.2</td>
</tr>
<tr>
<td>1-year mortality</td>
<td>7.03</td>
<td>11</td>
<td>2.9</td>
<td>2.8</td>
</tr>
</tbody>
</table>

THL: thrombolysis; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction. Continuous variables are expressed as means ± SD and qualitative variables are expressed in % *p < 0.05; **p < 0.001.
angiography was implemented in 96% of cases. The left ventricular ejection fractions at discharge were similar for the PPCI and THL groups. The 1-year mortality probability was the same for the 2 treatment groups for the overall population and for the patient subgroups aged [< 65 years]; [≥ 65 and < 75 years]. In contrast, the mortality was significantly higher for the patient subgroup [≥ 75 years] treated by THL.

**Time to treatment study**

The TT are shown in table 2. TT was significantly longer, about 1 hour longer, in the PPCI group than in the THL group (253 ± 133 vs. 191 ± 103 min, p = 0.0001). There was not statistically significant difference neither for the times to treatment of subgroups patients treated by PPCI nor for the times to treatment of subgroups patients treated by THL.

**Relationship between 1-year mortality, time to treatment and reperfusion strategy**

In the overall population, the 1-year mortality probability was positively and continually dependent on the TT for both treatment groups (figure 2). The logistic regression curves show that up to age 65 years, THL is superior to PPCI if the patients receive treatment within 2 hours of STEMI symptom onset. After that interval, PPCI is superior to THL, irrespective of the TT (figure 3 a). In the group of patients aged [≥ 65 and < 75 years], although there was no difference in terms of mortality, PPCI seems superior to THL irrespective of the TT (figure 3 b). From age 75 years, irrespective of TT, PPCI is consistently superior to THL (figure 3 c).

**Discussion**

Unlike the results of recent data (4), this study suggests on a 1-year mortality criteria that PPCI is not always upper than THL in patients with STEMI. More particularly, the study reminds the importance of TT and age on the results of reperfusion algorithm.

Both reperfusion strategies are positively correlated with TT but the results of PPCI are substantially less time to treatment-dependent than those of THL (figure 2). For PPCI, the plot is linear while it is exponential for THL (6). Mechanisms other than myocardial rescue such as a decrease in peri-infarct ischemia or a decrease in ventricular remodeling (7-9) may explain the benefit of late PPCI, unless the benefit is, in fact, relative and related to the inefficacy or negative effect of late THL (9). In addition, the difference in the slopes of the mortality curves as a function of TT indicates that the acceptable time to PPCI

### Table 2  Times to admission and treatment by age group and reperfusion strategy

<table>
<thead>
<tr>
<th>age (y)</th>
<th>overall</th>
<th>&lt; 65 y</th>
<th>65-74 y</th>
<th>&gt; 75 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPCI</td>
<td>THL</td>
<td>PPCI</td>
<td>THL</td>
</tr>
<tr>
<td>N</td>
<td>n=495</td>
<td>n=299</td>
<td>n=241</td>
<td>n=181</td>
</tr>
<tr>
<td>Time from onset of symptoms to admission (min)</td>
<td>189 ± 121</td>
<td>164 ± 87*</td>
<td>179±129</td>
<td>158±76*</td>
</tr>
</tbody>
</table>
| Time from onset of symptoms to start treatment (min) | 253 ± 133 | 191 ± 103** | 240±138 | 179±100** | 253±111 | 201±98* | 279±141 | 225±122*
| Time from admission to angioplasty treatment (min) | 65 ± 34 | - | 62±34 | - | 65±35 | - | 70±35 | - |
| Time from admission to thrombolysis (min) | - | 29 ± 44 | - | 30±36 | - | 26±43 | - | 38±75 |

The start of treatment was defined as the start of THL or the first balloon inflation. THL: thrombolysis; PCI: percutaneous coronary intervention. Intervals are expressed as means ± SD *p < 0.05; **p < 0.001

![Figure 2. Mortality as a function of time to treatment by reperfusion strategy](image-url)
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1-year death probability

A  
Age < 65 y

B  
Age ≥ 65 and < 75 y

C  
Age ≥ 75 y

Time to treatment (h)

Figure 3. Mortality curve as a function of time to treatment by reperfusion strategy
Panel A: patients aged < 65 years; Panel B: patients aged ≥ 65 years and < 75 years; Panel C: patients aged ≥ 75 years.

Implementation is not fixed but depends on the time to infarction management. For the same mortality probability, the time to treatment difference: [PPCI time to treatment - THL time to treatment] is variable. The later the patient receives care, the greater the acceptable time to implementing PPCI may be. That variability explains the difficulty encountered in determining the optimum time interval for PPCI implementation (PCI related delay = door to balloon - door to needle). Depending on the study, this delay ranges from 60 to 180 minutes (5, 10-12).

The logistic regression models for the patient subgroups show that, for each reperfusion strategy, the effect of TT on the 1-year mortality of STEMI patients varies greatly depending on patient age. Thus, for patients aged up to 65 years, THL implemented within 2 hours of STEMI symptom onset may be superior to PPCI. Subsequently, PPCI may be superior to THL, even if the patient’s door to balloon interval is greater than 90 minutes. These results concord with the PRAGUE 2 (13) and CAPTIM (14) data, for which the patients were young (mean age: 58 years) and the TT was particularly short (mean TT: 130 min). In patients aged ≥65 and < 75 years, although in the present study there was no difference in 1-year mortality, the profile of the mortality curves as a function of TT (figure 3b) are markedly different from those for patients aged less than 65 years. PPCI still seems to be a little superior to THL irrespective of the time to THL. These findings are consistent with the results of the DANAMI 2 study in which patients were older (mean age: 64 years) and the mean TT was much longer than in the CAPTIM study (169 minutes).

From age 75 years, PPCI is significantly superior to THL irrespective of the TT and including for STEMI treated very early (figure 3c). In that subgroup, the 1-year mortality of THL-treated patients was particularly marked, although the treatment was administered by cardiologists who were very conscious of the risk of such treatment. The prognosis of STEMI patients would appear to be more related to the type of reperfusion selected than to the TT (15-19). In that population, the ‘golden hour’ concept was not evidenced. The efficacy of THL could be compromised by a greater risk of bleeding, cerebrovascular accident or free wall rupture (20). Moreover, patient clinical risk profile of these patients is completely different with markedly more women, fewer smokers, more hypertension and more multi-vessels coronary disease that could participate to explain the poor benefit of THL in this subgroup. In those patients, it is even possible that THL does not confer any survival benefit or even worsens the prognosis, as has already been suggested elsewhere (21-22).

The age subgroup analysis showed that age modifies the impact of time to treatment on 1-year mortality for each reperfusion strategy. In line with Pinto’s findings (5), these arguments are in favor of incorporating age in the reperfusion algorithms, particularly since the datum is easy to obtain.

While THL is undeniably pertinent up to 65 years and in the first 2 hours post-STEMI symptom onset, further studies are needed to determine its position in the management algorithm for patients aged < 65 years after the first two hours after symptoms onset or in patients aged between 65 and 75 years when PPCI is possible. This issue will continue to be debated, particularly for as long as the results of combined therapy studies are not positive (23). For patients aged ≥ 75 years, THL should be used particularly carefully.
and the place of this treatment in this population needs to be revalued.

The present study has inherent limits due to its registry base. The small number of patients may be a limiting factor for the analysis. This study has not a sufficient statistical power to provide definite conclusion but aims to describe the interaction between TT and age in revascularization strategies. Patients were included over a long time period during which the medicinal treatment of STEMI has evolved. The fact that THL was mainly administered in the hospital was not, however, a limitation, since the measurement unit was the time to treatment and was thus independent of THL administration site.

Conclusion
TT and age remain two major parameters in reperfusion algorithms. TT affects patient prognosis differently, depending on the reperfusion strategy implemented and the patients’ cardiovascular risk, particularly age. While it is clear that THL is of value in the first 2 hours post-STEMI, it might be inappropriate after 75 years, irrespective of the time to symptom onset in patients aged up to 65 years, it might be not appropriate after 75 years, irrespective of the time to treatment. Furthermore, others studies are necessary to specify the reperfusion algorithms in other cases of STEMI.

References